REMARKS

The presently claimed invention features methods for identifying candidate compounds for modulating drug resistance of a cell and methods for determining whether a test compound modulates the drug resistance of a cell. The methods of the invention entail either determining whether a test compound alters the expression of MDA-9 in a cell or determining whether a test compound binds to MDA-9 and then measuring the effect of the test compound on the drug resistance of drug resistant cells in a non-human animal.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-3 as allegedly not enabled. According to the Examiner, the claims drawn to methods for identifying modulators of drug resistance by screening compounds for those that alter MDA-9 expression are not enabled because "not all genes isolated by differential screening based on drug resistance are part of the drug resistance mechanism and one cannot assume that the modulation of said genes and protein could reverse the drug resistant phenotype." To support the conclusion that MDA-9 is not involved drug resistance the Examiner cites Bertram et al. (*Anti-Cancer Drugs* 9:311, 1998). This publication identifies three genes--S110P, CAPL, and MAGE2--that are differentially expressed in doxorubicin-resistant and doxorubicin-sensitive cell lines. The Examiner suggests that the three genes are not involved in drug-resistance.

> S100P and CAPL are protein necessary for calcium metabolism, not drug resistance. MAGE is similarly not part of any molecular transporter or efflux pump mediating drug resistance.

The Examiner then goes on to state that the claims cannot be enabled without "objective evidence regarding the alteration of drug-resistance phenotype by a compound that modulated the level of expression or activity of MDA-9."

Applicants respectfully suggest that the Examiner's rejection is styled more as a rejection for lack of utility than lack of enablement. Surely, the Examiner does not doubt that one skilled in the art could screen compounds to identify those that alter MDA-9 expression and those which

bind to MDA-9. The specification clearly enables one skilled in the art to measure the expression MDA-9 in the presence and absence of a test compound. The specification also clearly enables one skilled in the art to measure whether a test compound binds to MDA-9. It seems likely that the Examiner has rejected the claims more for lack of utility than for lack of enablement or is using alleged lack of utility as a basis for alleged lack of enablement.

A *prima facie* showing of lack of utility can be made only when it can be established "that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial." Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098. Applicants respectfully submit that the Examiner has not made such a *prima facie* showing.

The Examiner cites Bertram et al. as evidence that not all genes that are differentially expressed in drug-resistant cells are actually part of a drug resistance mechanism. The Examiner notes that two of the genes identified by Bertram et al. as differentially expressed are involved in calcium metabolism. The Examiner appears be implying that a role in calcium metabolism is inconsistent with a role in drug resistance. However, this is simply the Examiner's unsupported assumption. Bertram et al. certainly make no such assumption. Indeed, Bertram et al. notes a number of different genes encoding proteins with a wide variety of functions are thought to be involved in mechanism of drug resistance. For example, on page 316, Bertram et al. notes that previously published studies have shown the insulin alters the distribution of the most prominent component of the MDR pathway and that proteins as disparate as calcium-binding proteins, proteins involved in alternative metabolic pathways, protein involved in protein degradation in the proteome, hormone receptors, proteins involved in detoxification, alternative polymerase subunits, and tumor associated antigens may all play a role in drug resistance. Moreover, Bertram et al. conclude that "[t]he genes identified in [Table 2] are mostly promising candidates for a role in the development of cellular drug resistance." Among the genes in Table 2 are S110P, CAPL, and MAGE2. Thus, it appears that Bertram et al. believe that the proposed functions of these three genes are <u>not</u> inconsistent with a role in drug resistance. Indeed, nearly all of the differentially expressed genes listed in Table 2 of Bertram et al. appear to encode proteins that are functionally related to the types of proteins that Bertram et al. states have been implicated in drug resistance. Thus, Bertram et al does not support the Examiner's assertion that

differential expression assays are not useful for identifying genes involved in drug resistance. Indeed, Bertram et al. suggests just the opposite proposition.

The Examiner stated that one of the genes identified by Bertram et al., MAGE3 is not "part of any molecular transporter or efflux pump mediating drug resistance." The Examiner appears to be suggesting that unless a protein is part of a "molecular transporter or efflux pump" it cannot mediate drug resistance. However, the publications noted by Bertram et al. clearly suggest that those skilled in the art do not believe that a protein must be part of a "molecular transporter or efflux pump" in order to mediate drug resistance. The Examiner has not supplied any evidence for his contrary conclusion.

The Examiner argued that "[w]ithout objective evidence regarding alteration of drug-resistance phenotype by a compound which modulated the level of expression or activity of MDA-9, one of ordinary skill in the art would be subject to undue experimentation, without reasonable expectation of success, in order to practice the claimed methods." Applicants believe that the Examiner is applying an improper standard. The Examiner is requiring more than would be needed to convince one of ordinary skill in the art that the claimed methods have a substantial and practical utility. As discussed above, the teachings of the specification and the knowledge of one of ordinary skill in the art would lead one to conclude that MDA-9 could be used to screen compounds for candidate modulators of drug resistance.

The Examiner also argued that the claims are not enabled because "[t]he specification does not describe in sufficient detail any proteins, peptides or small organic molecules which can bind to MDA-9 and thus alter the putative activity of MDA-9." The Examiner then goes on to argue that it is difficult to develop therapeutically useful antisense agents.

The Examiner's above-noted concerns are simply not relevant to the present claims. The present claims are drawn to screening methods that can be used to determine whether a test compound is a candidate or actual modulator of drug resistance in a cell. The Examiner's assertion that it is difficult to develop antisense molecules as therapeutic agents might be relevant if the Applicants were claiming therapeutic agents comprising antisense molecules, but they are not. Applicants are claiming screening methods. Indeed, the screening methods claimed are the very type of tool that can be used to address the challenges in developing therapeutic agents by providing an initial screening step to identify potentially useful compounds. The Examiner's

concerns related to the disclosure in the specification of "proteins, peptides or small organic molecules that can bind to MDA-9 and thus alter the putative activity of MDA-9" are similarly misguided. Applicants are not presently claiming such compounds. They are claiming screening methods that can be used to identify compounds that alter MDA-9 expression or cellular drug resistance.

In view of the forgoing, it is Applicants position that the present claims meet the requirements of 35 U.S.C. §101 and §112, first paragraph, and Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Conclusion

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claim 1 has been amended as follows:

1. (amended) A method for determining whether a test compound is a candidate modulator of [modulates] the drug resistance of a cell, the method comprising:

a) determining the level of MDA-9 expression in a cell in the presence of a test compound;

b) determining the level of MDA-9 expression in a cell in the absence of the test compound; and

c) identifying the compound as a [modulator] candidate modulator of drug resistance of the cell if the level of expression of MDA-9 in the cell in the presence of the test compound differs from the level of expression of MDA-9 in the cell in the absence of the test compound.